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Coffee consumption is associated with a lower risk of prostate cancer: a systematic review and meta-analysis

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Abstract

Objectives We aimed at conducting a meta-analysis of cohort studies to assess the association between coffee consumption and prostate cancer risk.

Data sources PubMed and Embase were searched for eligible studies up to Jan 2020.

Study selection Cohort studies were included.

Data extraction and synthesis Data synthesis was undertaken via systematic review and meta-analysis of available evidence. All review stages were conducted independently by 2 reviewers.

Main outcomes and measures Prostate cancer was the main outcome, which were classified as follows: localized prostate cancer which included localized or nonaggressive cancers, advanced prostate cancer which included advanced or aggressive cancers, and fatal prostate cancer which included fatal/lethal cancers or prostate cancer specific deaths.

Results Fifteen prospective cohort studies, with 50,200 cases of prostate cancer and 949,752 total cohort members, were included in the meta-analysis. A statistically significant inverse association was detected between coffee consumption and prostate cancer risk. The pooled relative risk (RR) was 0.91 (95% CI: 0.84, 0.98; I^{2}= 53.2%) for the highest coffee consumption compared with lowest consumption. The association exhibited a linear trend (P =0.006 for linear trend), and the pooled RR was 0.989 (95% CI: 0.982, 0.997) for an increase of 1 cup of coffee per day. The pooled RRs were 0.93 (95% CI: 0.87, 0.99), 0.88 (95% CI: 0.71, 1.09) and 0.84 (95% CI: 0.66, 1.08) for localized, advanced and fatal prostate cancer, respectively. No

publication bias was detected.

Conclusions Our findings provide more evidence that increased coffee consumption is associated with lower prostate cancer risk. It implies that men might be encouraged to increase the coffee intake to lower their risk of prostate cancer.

Strengths and limitations of this study

- Prospective cohort design of the included studies should have eliminated the selection and recall bias.
- Large sample size could provide sufficient statistical power to assess even a relatively small effect.
- Residual confounding inherent in the original studies may distort the association between coffee consumption and prostate cancer.
- Misclassification of coffee consumption may occur due to the self-reported nature of the exposure.
- Significant heterogeneity among studies results may come from various sources.

INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, with an estimated 1,276,000 new cancer cases and 359,000 cancer deaths in 2018.[1] Nearly three-quarters of the registered cases occur in developed countries.[1] Since 1970s, the incidence of prostate cancer has also increased rapidly in some Asia countries, such as China, Singapore and Japan, where the incidences have always been much lower than some Western countries.[1,2] As such, primary prevention of prostate cancer is therefore a critical public health challenge worldwide.

Coffee is one of the most widely consumed beverages in the world. Since its popularity continues to increase worldwide, even small effects of coffee on individuals may exert a large effect on public health. Coffee is known to be a major source of dietary caffeine, cafestol and antioxidants in industrialized nations.[3] Its various constituents such as caffeine, caffeic acid and chlorogenic acid can potentially impact the development of cancer of various sites through multiple pathways, from carcinogenesis to cellular apoptosis.[4,5] Inverse associations were observed between coffee consumption and the risk of cancer in sites such as the liver, colorectum and breast.[6] However, previous studies of the association between coffee consumption and prostate cancer risk have produced inconsistent results. Although earlier prospective studies did not detect an association,[7-15] more recent studies conducted in some Western countries including the United States, Sweden and the United Kingdom reported that coffee consumption was associated with a lower risk of localized and advanced prostate cancer.[16-20] In Japan, a country with increasing popularity of coffee, a cohort study also found a significant inverse association between coffee consumption and the risk of prostate cancer.[21]

Previous meta-analysis of cohort studies up to 2015 reported a significant positive association for coffee consumption on total prostate cancer risk, with highly varied results in different subgroups,[22,23] Since then, four cohort studies have explored the association, but still reported inconsistent results.[24-27] Thus, we conducted a meta-analysis with the most up-to-date evidence from prospective cohort studies to assess the association between coffee consumption and prostate cancer risk, and expected to direct future primary prevention strategy on prostate cancer.

METHODS

Patient and Public Involvement

No patients eligible for screening were involved in the design and conduct of the study or involved in defining the research question or outcome measures. We have no intentions to disseminate our results to patients eligible for screening.

Study Selection

This systematic review was reported using PRISMA guidelines;[28] the PRISMA checklist is provided as **Supplementary Table S1**. A literature search up to Jan 2020 was performed using PubMed and Embase with the following key words: coffee and prostate and (cancer or carcinoma or neoplasm or tumor). The identified publications were reviewed independently for their relevance to the research topic by two authors.

We also manually searched the reference lists of relevant publications to identify additional studies. To be included in the meta-analysis, studies had to: (a) use an observational, prospective cohort design, (b) present information on coffee consumption as the exposure of interest, (c) report prostate cancer as the outcome of interest, and (d) provide relative risk (RR)/ hazard ratio (HR) estimates with confidence intervals (CIs) or standard errors. Instances in which data were insufficient or missing, we attempted to contact the authors of the articles to request the relevant data, and then two authors provided us with the relevant information about the person-years of follow-up for specific categories of coffee intake to facilitate the dose-response analyses. [15,20]

We used the reported relative risk as the measure of the association between coffee consumption and the risk of prostate cancer. If multiple estimates were provided, priority was given to the multivariable adjusted risk estimates. If more than one study was conducted in the same population, we selected the most recent report.

Data Extraction and Study Quality Assessment

We abstracted the following data from each publication: the first author's name, the year of publication, the country in which the study was performed, the duration of follow-up, the size of the cohort, the number of prostate cancer cases, the assessment of coffee consumption, the primary study outcome, the categories of coffee consumption, the RRs and 95% CIs for all prostate cancer outcomes associated with coffee consumption and the covariates included for adjustment in multivariable models.

The Newcastle-Ottawa Scale was used to assess study quality. [29] Study was judged on 3 broad categories for cohort studies as follows: the selection of study groups, comparability of groups, and ascertainment of either the exposure or outcome of interest.

Statistical Analysis

We pooled the RR estimates for the highest versus the lowest coffee consumption category from each study. We used a fixed effect model to pool the study specific estimates unless significant heterogeneity was observed, then the random effect model proposed by DerSimonian and Laird was used.[30] Additionally, we conducted analyses stratified by study location and prostate cancer stage. Based on definitions of each original studies, the prostate cancer categories were classified as follows: (1) localized prostate cancer which included localized or nonaggressive cancers, (2) advanced prostate cancer which included advanced or aggressive cancers, (3) fatal prostate cancer, a subset of advanced prostate cancer, which included fatal/lethal cancers or prostate cancer specific deaths. We also conducted analyses stratified by whether the studies adjusted for potentially important confounders including history of prostate-specific antigen (PSA) testing, a family history of prostate cancer, total energy intake, smoking status, alcohol consumption, physical activity, body mass index (BMI), or history of diabetes. Since PSA testing was generally introduced after 1986,[31] studies with follow-up periods that ended before 1986 were classified in the PSA-adjusted group. We also performed a sensitivity analysis of the influence of individual studies on the summary estimate by repeating the meta-analysis excluding one study at a time.

We further examined the potential dose-response relationship between coffee consumption and the risk of prostate cancer. Twelve studies had sufficient information for the dose-response analyses. The pooled relative risk for an increase of 1 cups of coffee per day was estimated using a procedure described by Orsini and Greenland.[32] We examined a potential nonlinear relation between coffee consumption and prostate cancer risk by modeling coffee consumption using restricted cubic splines for nonlinear trends with 4 knots at fixed percentiles (5%, 35%, 65%, and 95%) of the distribution.[33] A P value for nonlinearity was computed by testing the null hypothesis that the coefficients of the second and third splines which represent the non-linear component are equal to zero.

Heterogeneity among studies was assessed with the Q and the I^2 statistic and results were defined as heterogeneous for a P value <0.10 or an I^2 >50%.[34] Small study effects such as publication bias were evaluated by Begg's and Egger's tests.[35,36] Statistical analyses were conducted using Stata version 14.0 (StataCorp LP, College Station, Texas). Two-sided P values <0.05 were considered statistically significant.

RESULTS

Literature Search

A total of 316 records were identified from the two databases, of which 291 records were excluded after review of the titles and abstracts based on the pre-specified inclusion criteria. After reviewing the full text of the remaining 25 cohort studies, 10 studies were excluded as no useful risk estimates or 95% CIs were reported. Two studies were excluded as newer data was available. Thirteen studies were obtained from full-text screening. In addition, two studies were identified by checking the reference lists of retrieved articles Thus, we included 15 studies in the final analysis [9-11,13-19,21,24-27]. **(Figure 1)**

Study Characteristics and Quality Assessment

Descriptive data for the studies included in our analysis are summarized in **Supplementary Table S2.** The included studies were conducted in the North America (n=7), Europe (n=6), Japan (n=2). There were a total of 949,752 men in the 15 cohort studies, of whom 50,200 developed prostate cancer. To measure coffee consumption, 11 studies used food-frequency questionnaires and four used a self-administered dietary questionnaire. Most studies included adjustment for the most potential confounders, such as age, family history of prostate cancer, race, smoking, alcohol consumption, total energy intake, body mass index (BMI), and physical activity, et al. Study-specific quality scores are summarized in **Supplementary Table S3**. The quality scores ranged from 6 to 9, and most studies were assessed as high quality studies.

Overall Analyses and Dose-Response Analyses

As shown in **Figure 2**, the overall analysis of 15 studies showed a 9% reduction in the risk of prostate cancer for high consumption of coffee (RR=0.91; 95% CI: 0.84, 0.98), with statistical significant heterogeneity (P=0.008, I^2=53.2%). In dose-response analyses, we found evidence of a linear inverse association between coffee consumption and prostate cancer risk (*P*=0.006 for linear trend) (**Figure 3**). The pooled RR of prostate cancer was 0.989 (95% CI: 0.982, 0.997) for an increase of 1 cup of coffee per day. There was no evidence of a nonlinear relation between coffee consumption and risk of prostate cancer (*P*=0.193 for non-linearity). There was no indication of small study effects such as publication bias either from the results of Egger's test (*P*= 0.409) or Begg's test (*P*= 0.843) (**Supplementary Figure S1**).

Subgroup and Sensitivity Analyses

The effects of coffee consumption on prostate cancer risk in subgroup analyses are shown in **Table 1**. For localized prostate cancer, there was a 7% reduction in risk for high consumption of coffee (RR=0.93; 95% CI: 0.87, 0.99). The pooled RRs were 0.88 (95% CI: 0.71, 1.09) and 0.84 (95% CI: 0.66, 1.08) for advanced and fatal prostate cancer, respectively. When stratified by study location, the pooled RRs were 0.96 (95%CI: 0.90 , 1.03), 0.85 (95%CI: 0.74 , 0.98) and 0.85 (95%CI: 0.48 , 1.51) for studies conducted in North America (six in the United States and one in Canada) and European countries and Japan. When we stratified studies by adjustment for specific confounders, significant inverse associations were observed in all of the confounder adjusted subgroups.

In sensitivity analyses, we recalculated the pooled RRs by sequentially excluding one study. The study-specific RRs ranged from 0.89 (95% CI: 0.82, 0.97) to 0.93 (95% CI: 0.86, 1.00) after omissions of Hashibe et al. and Terdal et al., respectively.

Table 1. Summary estimates and corresponding 95% confidence intervals for coffee consumption and prostate cancer

	No. of	Summary	95% CI	I^2 (%)	*P*

	studies	RR			value [a]
High versus low consumption	15	0.91	(0.84 , 0.98)	53.2	0.008
Prostate cancer category [2]					
Localized	6	0.93	(0.87 , 0.99)	37.0	0.159
Advanced	8	0.88	(0.71 , 1.09)	52.7	0.039
Fatal	6	0.84	(0.66 , 1.08)	46.3	0.097
Study location					
North America	7	0.96	(0.90 , 1.03)	17.7	0.295
Europe	6	0.85	(0.74 , 0.98)	63.3	0.018
Japan	2	0.85	(0.48 , 1.51)	68.5	0.075
Study quality					
High	9	0.87	(0.79 , 0.98)	69.4	0.001
Low	6	1.06	(0.89 , 1.26)	0	0.917
Adjustment for confounders					
PSA testing [c]					
Yes	6	0.86	(0.77 , 0.96)	31.8	0.197
No	9	0.94	(0.84 , 1.06)	60.5	0.009
Family history of prostate cancer					
Yes	4	0.83	(0.72 , 0.96)	57.8	0.068
No	11	0.95	(0.85 , 1.05)	50.8	0.026
Total energy intake					
Yes	6	0.85	(0.76 , 0.96)	61.1	0.025
No	9	0.97	(0.85 , 1.09)	47.7	0.053
Smoking status					
Yes	10	0.86	(0.79 , 0.94)	52.0	0.027
No	5	1.03	(0.95 , 1.11)	0	0.805
Alcohol consumption					
Yes	6	0.87	(0.84 , 0.98)	49.2	0.008
No	9	0.93	(0.84 , 1.03)	57.2	0.017
Physical activity					
Yes	7	0.87	(0.79 , 0.95)	58.4	0.025
No	8	1.00	(0.90 , 1.12)	10.5	0.348
BMI					
Yes	9	0.86	(0.78 , 0.94)	56.9	0.017
No	6	1.03	(0.95 , 1.11)	0	0.897
Diabetes					
Yes	5	0.87	(0.84 , 0.98)	64.9	0.022
No	10	0.97	(0.86 , 1.10)	22.8	0.233

[a] *P*-value for heterogeneity within each subgroup.

RR, relative risk; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen.

DISCUSSION

In this meta-analysis, increased coffee consumption was significantly associated with a reduced risk of prostate cancer in men. In the dose-response analysis, a nearly 1% reduction in risk of prostate cancer was observed for an increase of 1 cup of coffee per day. The combined estimate for prostate cancer was robust across sensitivity analyses and no publication bias was detected.

Previous meta-analysis detected a statistically significant positive association between coffee consumption and prostate cancer risk (RR=1.16; 95% CI: 1.01, 1.33).[22] However, this observed effect was confined to the case-control studies (RR=1.21; 95% CI: 1.03, 1.43), and no significant association in the cohort studies (RR=1.06; 95% CI: 0.83, 1.35) when stratified by study design.[22] Considering the case-control design patients with prostate cancer might differentially recall their past coffee consumption habits compared to healthy controls which might generally lead to biased estimates. This potential recall bias could generate a spurious positive association between coffee consumption and prostate cancer risk. Additionally, selection bias which can occur in case-control studies may distort the association between coffee consumption and prostate cancer risk. In another meta-analysis of cohort studies with 539,577 participants and 34,105 cases, the pooled RR for the highest vs. lowest coffee intake was 0.90 (95% CI: 0.85-0.95) for total prostate cancer. In the current updated meta-analysis of 949,752 cohort members and 50,200 cases, the overall result was similar with the previous one, but for subgroups of localized, advanced and fatal prostate cancers, the strength of associations tended to be weaker compared with the previous study.

An inverse association between coffee and risk of prostate cancer is biologically plausible. Coffee improves glucose metabolism, decreases concentrations of plasma insulin and insulin-like growth factors-1, has anti-inflammatory and antioxidant effects, and affects sex hormone levels, all of which may play roles in the initiation, development and progression of prostate cancer.[3,18,20,37] Coffee is also a major source of chlorogenic acids; intake of quinides, the degradation products of chlorogenic acids, has been observed to increase insulin sensitivity and lower blood glucose levels.[3] Moreover, coffee intake has been shown to be associated with higher adiponectin plasma levels,[38,39] an endogenous insulin sensitizer.[40] Higher adiponectin plasma levels lead, in turn, to decreased concentrations of plasma insulin.[40] In two prospective studies, insulin levels were observed to be directly associated with prostate cancer specific mortality.[41,42]

Coffee is a major contributor of dietary antioxidants such as caffeic acid and chlorogenic acid.[20] A prospective cohort study from the United States found that dietary antioxidants from coffee, e.g. the caffeic acid, were inversely associated with risk of total, advanced and lethal prostate cancer,[20] Additional research has led to the conclusion that antioxidants protect cells from damage caused by oxidative stress and its associated pathological conditions including inflammation which is a precursor of neoplastic transformation in the prostate.[43] Additionally, preclinical studies have shown that dietary antioxidants may slow or prevent prostate cancer progression through oxidative stress reduction which is generally considered a key event in the initiation, development and progression of prostate cancer.[43] Coffee drinking may be associated with increased sex hormone-binding globulin (SHBG) and total testosterone levels.[44,45] A pooled analysis of 18 prospective studies found an inverse association between SHBG levels and prostate cancer incidence.[37] Of note, a nested case-control study found that caffeine and caffeinated coffee intakes were positively associated with plasma SHBG levels, but with no association between decaffeinated coffee and plasma SHBG levels which suggested that caffeine may be the key component of coffee responsible for determining plasma SHBG levels.[45]

A strength of this meta-analysis was the prospective cohort design of the included studies, which should have eliminated the selection and recall bias that could be of concern from case-control studies. In addition, the large number of total cohort members and prostate cancer cases could provide sufficient statistical power to assess even a relatively small effect of coffee consumption on prostate cancer risk. Furthermore, we were able to conduct the dose-response analysis support the hypothesis of an inverse linear association between coffee consumption and risk of prostate cancer. Our study also has some limitations. Because of the observational design, residual confounding may distort the association between coffee consumption and prostate cancer and we were not able to address problems with confounding inherent in the original studies. For example, the inverse association between coffee consumption and prostate cancer could be attributed to other factors related to coffee consumption, such as family history of prostate cancer, physical exercise, or other healthy habits and dietary factors. However, most studies included in this meta-analysis adjusted for at least some of the major potential confounders. When we restricted the analysis to studies that adjusted for the potential confounders, the magnitude of the associations in the subgroups tended to be larger in comparison with the overall association. Another limitation is misclassification of coffee consumption, due to the self-reported nature of the exposure in the included studies. However, results from validation studies indicated that coffee consumption was assessed with relatively high validity. The correlations between coffee consumption assessed by questionnaire and diet records were 0.80 in US men,[16] 0.71 in Swedish men,[17] and 0.72 in Japanese men.[21] In cohort studies, even if misclassification occurred, it would most likely be non-differential and would bias results toward the null. Therefore, the association between coffee consumption and risk of prostate cancer may be even stronger. Finally, there was significant heterogeneity among studies results. There are several potential explanations for the observed between-study heterogeneity. First, the range of coffee consumption between the high and low category varied between studies. The risk estimates would be assumed to be higher in studies with broader ranges of coffee consumption. Second, the type of coffee and different brewing methods included in the coffee consumption groups differed. Third, the size of cohort and the length of follow-up varied from study to study. Because the strength of the association differed between studies, which resulted in statistical heterogeneity, the summary risk estimates should be interpreted with caution.

CONCLUSIONS

This meta-analysis demonstrated that an increased coffee consumption is associated with a reduced risk of prostate cancer. These findings add to and extend the evidence that increased coffee consumption may have protective effects on prostate cancer; thus, men should be encouraged to increase their coffee consumption to potentially decrease their risk of prostate cancer. Moreover, the underlying mechanisms and active compounds in coffee that are responsible for this association remain to be further elucidated.

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AUTHOR CONTRIBUTIONS Kefeng Wang obtained the funding, developed the research design, interpreted the results, and also had primary responsibility for the final content; Xiaonan Chen, Yiqiao Zhao, Zijia Tao analyzed the data and interpreted the results; Xiaonan Chen and Kefeng Wang drafted manuscript; all authors critically reviewed and approved the manuscript.

COMPETING INTERESTS STATEMENT: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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DATA SHARING

No additional data are available.

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Table

Table 1. Summary estimates and corresponding 95% confidence intervals for coffee consumption and prostate cancer

Figure legends

Figure 1 Flow diagram of study selection in the meta-analysis.

Figure 2 Forest plot for the association between coffee consumption and prostate cancer risk.

Figure 3 Dose-response relationship of coffee consumption with prostate cancer risk.

Supplementary Material

Table S1 PRISMA 2009 checklist.

Table S2. Characteristics of cohort studies of coffee consumption and prostate cancer risk included in the meta-analysis.

Table S3 Quality of cohort studies included in the meta-analysis.

Figure S1 Funnel plot of coffee consumption and prostate cancer risk**.**

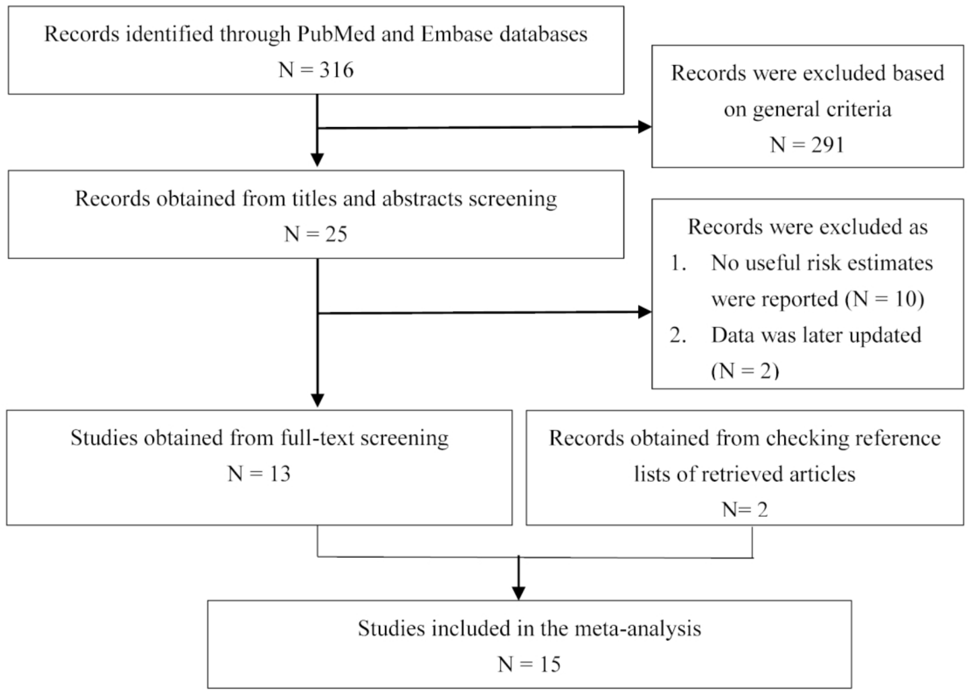

Figure 1 Flow diagram of study selection in the meta-analysis.

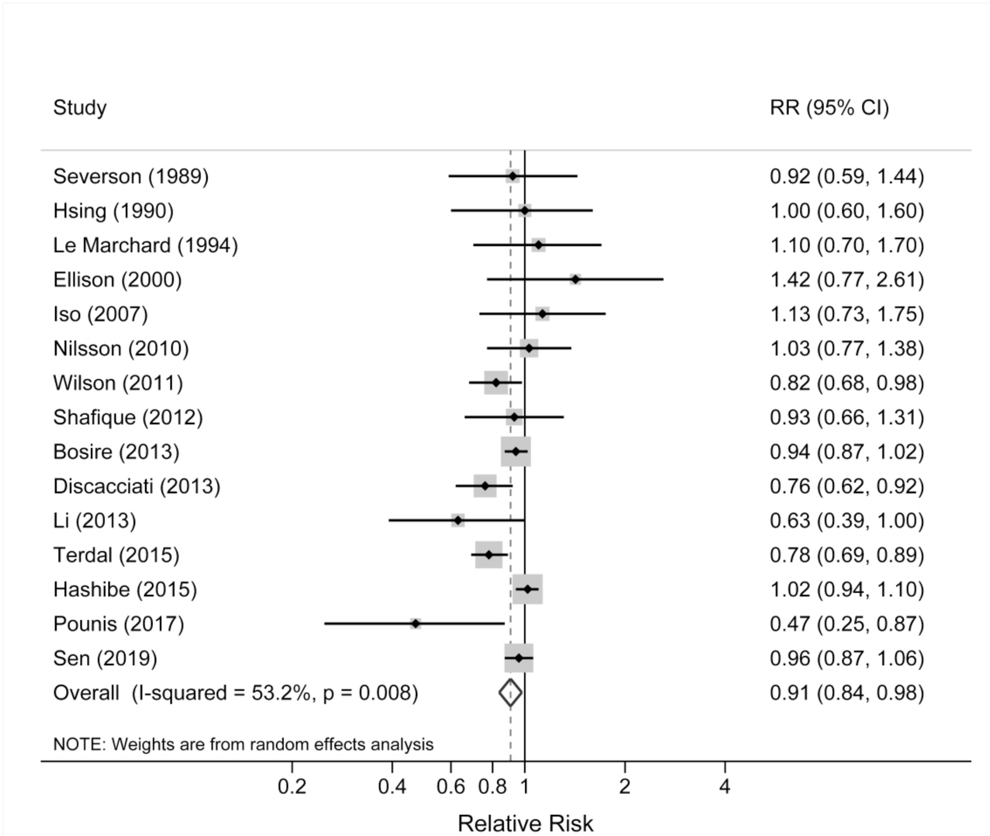

Figure 2 Forest plot for the association between coffee consumption and prostate cancer risk.

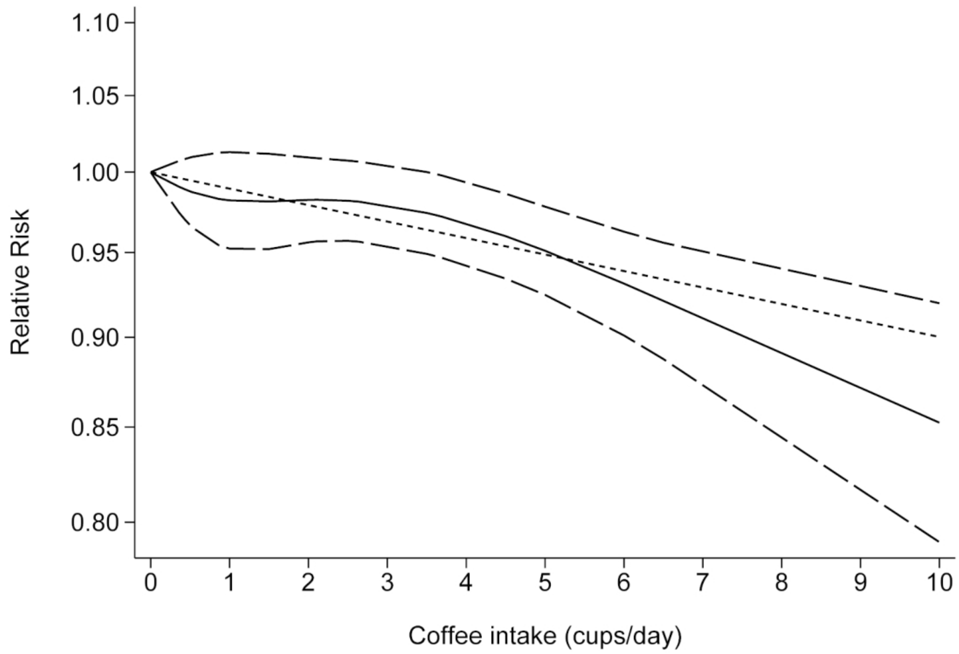

Figure 3 Dose-response relationship of coffee consumption with prostate cancer risk.

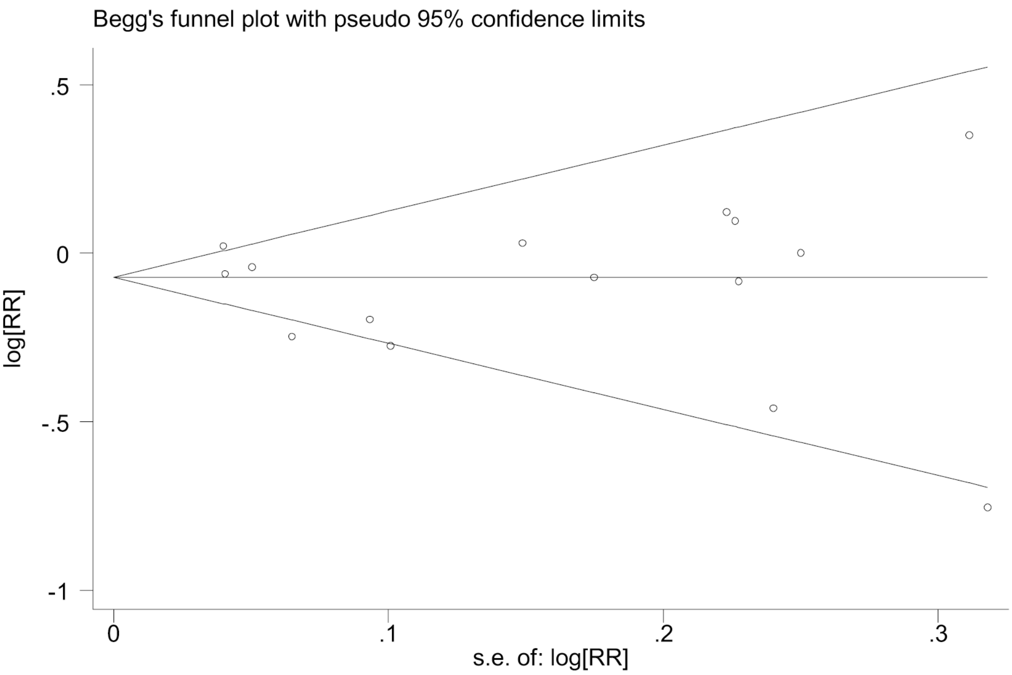
Begg's funnel plot with pseudo 95% confidence limits
.5
0
-.5
-1
log[RR]
0
.1
.2
.3
s.e. of: log[RR]

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4，5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5，6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7，8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present the main results of the review. If meta-analysis are done, including for each, confidence intervals and measures of consistency.	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9，10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14,15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary Table S2. Characteristics of cohort studies of coffee consumption and prostate cancer risk included in the meta-analysis

Study	Country	Study period	Size of cohort	No. of cases	Assessment of coffee consumption	Outcome	Adjustments
Sen et al. 2019	Europe	1990s-2015	142196	7036	Validated FFQ	Total, Localized, advanced prostate cancer	Stratified by center and age at recruitment in 5 years categories, and adjusted for smoking status, BMI, history of diabetes, alcohol intake, education, physical activity, energy intake, as well as calcium, fish, tea, fruit and vegetable intake.
Pounis et al 2017	Italy	2005-2010	6989	100	Validated FFQ	Total prostate cancer	Age, energy intake, smoking habits and BMI
Hashibe et al. 2015	USA	1992-2011	46771	3037	Validated diet history questonnaire	Total prostate cancer	Age, sex, race, and education.
Tverdal et al. 2015	Norway	1985-1999	224234	5740	Questionnaire	Total prostate cancer	Age, smoking, BMI, height, physical activity, total cholesterol, triglycerides, systolic blood pressure, year of examination and diabetes
Li et al. 2013	Japan	1995-2005	18,853	318	Validated FFQ	Total prostate cancer incidence	Age, education, BMI, time engaging in sports or exercise, marital status, time spent walking, smoking status, family history of cancer, job status, total energy intake, passive smoking, alcohol drinking, daily consumption of miso soup
Discacciati et al. 2013	Sweden	1998-2010	44,613	3801	Validated self-administered FFQ	Localized and advanced prostate cancer incidence Prostate cancer mortality	Age, tea, alcohol, BMI, diabetes, family history of prostate cancer, smoke, physical activity, education, total energy intake.

Bosire et al. 2013	USA	1995-2008	288,391	23335	Validated FFQ	Total prostate cancer incidence	Age, race, height, BMI, physical activity, smoking, history of diabetes, family history of prostate cancer, PSA testing, intakes of tomato sauce, alpha-linolenic acid, and total energy intake.
Shafique et al. 2012	UK	1970-2007	6017	318	Self-administered questionnaire	Total prostate cancer incidence	Age at screening, cholesterol, systolic blood pressure, BMI, alcohol intake, tea consumption, smoking status, social class.
Wilson et al. 2011	USA	1986-2006	47,911	5035	Validated FFQ	Total prostate cancer incidence	Age in months, calendar time, race, BMI at age 21, current BMI, vigorous physical activity, smoking, diabetes, family history of prostate cancer in father or brother, multivitamin use, intakes of processed meat, tomato sauce, calcium, alpha-linolenic acid, supplemental vitamin E, alcohol intake, energy intake, history of PSA testing.
Nilsson et al. 2010	Sweden	1985-2007	30,930	653	Semi-quantitative FFQ	Total prostate cancer incidence	Age, BMI, smoking, education, recreational physical activity.
Iso et al. 2007	Japan	1990-2003	43,500	161	Validated FFQ	Prostate cancer mortality	Age, area of study
Ellison et al. 2000	Canada	1970-1993	3400	145	FFQ	Total prostate cancer incidence	Age, wine consumption.
Le Marchand et al. 1994	USA	1975-1989	20,316	198	Self-administered life-style questionnaire	Total prostate cancer incidence	Age, ethnicity, income.
Hsing et al. 1990	USA	1966-1986	17,633	149	FFQ	Prostate cancer mortality	Age, tobacco use.

Severson et al. 1989	USA	1965-1986	7998	174	FFQ + 24-h diet recall interview	Total prostate cancer incidence	Age

FFQ, food frequency questionnaire; RR, relative risk; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen

Supplementary Table S3 Quality of cohort studies included in the meta-analysis

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Controls for important risk factors [1]	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total quality score
Sen et al. 2019	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Pounis et al 2017	☆	☆	☆	☆	☆☆	☆	-	☆	8
Hashibe et al. 2015	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Terdal et al. 2015	☆	☆	-	☆	☆☆	☆	☆	☆	8
Li et al. 2013	☆	☆	☆	☆	☆☆	☆	☆	-	8
Discacciati et al. 2013	☆	☆	☆	☆	☆☆	☆	☆	-	8
Bosire et al. 2013	☆	☆	☆	☆	☆☆	☆	☆	-	8
Shafique et al. 2012	☆	☆	-	☆	☆☆	☆	☆	☆	8
Wilson et al. 2011	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Nilsson et al. 2010	☆	☆	☆	-	☆☆	☆	-	☆	7
Iso et al. 2007	☆	☆	-	☆	☆	☆	☆	-	6
Ellison et al. 2000	☆	☆	☆	☆	☆	☆	☆	-	7
Le Marchand et al. 1994	☆	☆	☆	☆	☆	☆	☆	-	7
Hsing et al. 1990	☆	☆	-	☆	☆	☆	☆	☆	7
Severson et al. 1989	☆	☆	☆	☆	☆	☆	☆	-	7

1. A maximum of 2 stars could be awarded for this item. Studies that included adjustment for age received one star, and studies that included most of the other important confounders such as ethnicity, dietary factors (energy intake, vitamin D, dietary fat etc.), physical activity, body mass index, type 2 diabetes mellitus, alcohol and smoking received an additional star.

Coffee consumption and risk of prostate cancer: a systematic review and meta-analysis

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Urology
Keywords:	EPIDEMIOLOGY, Prostate disease < UROLOGY, Nutrition < TROPICAL MEDICINE

Coffee consumption and risk of prostate cancer: a systematic review and meta-analysis

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Key words: Coffee; Prostate cancer; Cohort studies; Meta-analysis; Dose-response relationship

Word count: Text = 3561 words

Abstract

Objectives We aimed at conducting a systematic review with meta-analysis of cohort studies to evaluate the association of coffee consumption with risk of prostate cancer.

Data sources We searched PubMed, Web of Science and Embase for eligible studies up to September 2020.

Study selection Cohort studies were included.

Data extraction and synthesis Two researchers independently reviewed the studies and extracted the data. Data synthesis was performed via systematic review and meta-analysis of eligible cohort studies. Meta-analysis was performed with the "*metan*" and "*glst*" commands in Stata 14.0.

Main outcomes and measures Prostate cancer was the main outcome. It was classified as localized prostate cancer which included localized or nonaggressive cancers; advanced prostate cancer which included advanced or aggressive cancers; or fatal prostate cancer which included fatal/lethal cancers or prostate cancer specific deaths.

Results Sixteen prospective cohort studies were finally included, with 57,732 cases of prostate cancer and 1,081,586 total cohort members. Higher coffee consumption was significantly associated with lower risk of prostate cancer. Compared with lowest category of coffee consumption, the pooled relative risk (RR) was 0.91 (95% CI: 0.84, 0.98; I^2= 53.2%) for the highest category of coffee consumption. There was a significant linear trend for the association (P =0.006 for linear trend), with a pooled RR of 0.988 (95% CI: 0.981, 0.995) for each increment of 1 cup of coffee per day.

42 For localized, advanced and fatal prostate cancer, the pooled RRs were 0.93 (95% CI: 0.87, 0.99), 0.88 (95% CI: 0.71, 1.09) and 0.84 (95% CI: 0.66, 1.08), respectively. No evidence of publication bias was indicated in this meta-analysis.

Conclusions This study suggests that higher intake of coffee may be associated with lower risk of prostate cancer.

Strengths and limitations of this study

- Risk of selection and recall bias may be minimized due to the inclusion of prospective cohort studies.
- Large sample size ensures adequate statistical power to detect even a small effect of interest.
- Uncontrolled/residual confounding may distort the association between coffee consumption and prostate cancer.
- Misclassification of coffee consumption may occur due to the self-reported nature of the exposure.
- Significant heterogeneity among studies results may come from various sources.

INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males. There were 1,276,000 new cancer cases and 359,000 cancer deaths in 2018.[1] It is estimated that nearly three-quarters of prostate cancer cases occur in developed countries.[1] Since the 1970s, the incidence of prostate cancer has also increased rapidly in some Asia countries, such as China, Singapore and Japan, where the incidences have always been much lower than some Western countries.[1 2] Therefore, primary prevention of prostate cancer is a significant public health problem worldwide.

Coffee is one of the most popular beverages. Since its popularity continues to increase worldwide, even a small effect on individual health may exert substantial public health impact. Coffee is known to be a major source of dietary caffeine, cafestol and antioxidants in industrialized nations.[3] Its various constituents such as caffeine, caffeic acid and chlorogenic acid can potentially impact the development of cancer through multiple carcinogenesis pathways.[4 5] Inverse associations were observed between coffee consumption and the risk of cancer in sites such as the liver, colorectum and breast.[6] However, previous studies have reported inconsistent results on the association of coffee consumption with risk of prostate cancer. Although earlier cohort studies did not detect an association,[7-15] more recent studies conducted in major Western countries, such as the US, Sweden and the United Kingdom, reported that coffee consumption was associated with a lower risk of localized and advanced prostate cancer.[16-20] In Japan, a country with increasing popularity of coffee, a cohort study also found a significant inverse association between coffee consumption and the risk of prostate cancer.[21]

Previous meta-analysis of cohort studies up to 2015 reported a significant positive association for coffee consumption on total prostate cancer risk, with highly varied results in different subgroups,[22 23] Since then, five cohort studies have explored the association, but still reported inconsistent results.[24-28] It was hypothesized that higher coffee consumption was associated with increased risk of prostate cancer. Thus, the objective of this updated meta-analysis was to explore and evaluate the association of coffee intake with risk of prostate cancer in adult men, and expected to direct future primary prevention strategy on prostate cancer.

METHODS

This systematic review was conducted and reported in adherence to the PRISMA and the MOOSE guidelines;[29] the corresponding checklists were provided as **Supplementary Document 1 and Supplementary Document 2**. Two researchers (YQZ and ZJT) independently conducted the literature search, study selection, data extraction and study quality assessment. Any discrepancies were resolved by discussion, but whenever consensus cannot be reached between the two reviewers, a third reviewer (KFW) acted as arbitrator.

Patient and public involvement

This is a meta-analysis based on study-level data and no individual-level data were involved in the study or involved in defining the research question or outcome measures.

Inclusion criteria

Eligibility criteria of the studies were determined as follows: (1) study should use a longitudinal cohort design, or case-control design nested within a cohort study. (2) Study should present information on coffee consumption as the exposure of interest. Coffee consumption was ascertained by self-reported dietary records or food diaries on the intake levels (highest intake category vs lowest intake category) or frequency measures (e.g. per unit/cups/ml per day/week). Since the intake levels were classified and defined differently in each study, the absolute coffee consumption in the highest and lowest intake categories varied across the included studies. (3) Study should report prostate cancer as the outcome of interest. The prostate cancer was defined by clinical diagnosis, physician diagnosis, medical records, self-reports, or data linkage to registry system such as a cancer registry. Based on definitions in each original study, the prostate cancer categories were classified as follows: (i) localized prostate cancer which included localized or nonaggressive cancers, (ii) advanced prostate cancer which included advanced or aggressive cancers, (iii) fatal prostate cancer which included fatal/lethal cancers or prostate cancer specific deaths. (4) Study should provide relative risk (RR), hazard ratio (HR), risk ratio, rate ratio or odds ratio estimates with confidence intervals (CIs) or standard errors for the association of coffee consumption with risk of prostate cancer. If multiple estimates were provided, priority was given to the multivariable-adjusted risk estimates. If more than one study was conducted in the same population, we excluded the earlier reports or reports with less applicable information.

Literature search

A literature search was performed using PubMed, Web of Science and Embase up to September 2020 with the following key words: coffee and prostate and (cancer or carcinoma or neoplasm or tumor). The full search strategy was shown in **Supplementary Document 3**. The reference lists of relevant publications were also manually searched for identification of additional eligible studies. No language limitation was imposed.

When data or information in the publication were insufficient, we attempted to contact the corresponding authors of the original study to request the relevant data. Then two authors (Russnes and Nilsson) provided us with the relevant information about the person-years of follow-up for specific categories of coffee intake to facilitate the dose-response analyses. [15 20] Of note, we finally did not include the Russnes et al. study [20] in the current meta-analysis because the study population are the same with another included cohort study (Wilson et al. study) [18] which reported more applicable information.

Data extraction

We extracted the following information from each eligible study: the first author's name, the year of publication, the study country, the follow-up time, the number of participants in cohort, the number of prostate cancer cases, the assessment of coffee consumption, the primary study outcome, the definitions and categories of coffee consumption, the RRs and 95% CIs for all prostate cancer outcomes associated with coffee consumption, and the potential confounders considered or adjusted in the analysis.

Study quality assessment

The 9-star Newcastle-Ottawa Scale tool was used to assess study quality. [30] The quality of each cohort study was judged on three broad categories including the selection of study population, comparability of groups, and ascertainment of either the exposure or outcome of interest.

Statistical analysis

In the meta-analysis, the RR estimate was used to measure the association between coffee consumption and the risk of prostate cancer in this meta-analysis. We pooled the study-specific RR estimates for the highest versus the lowest category of coffee consumption. Fixed effects model was employed to pool the study-specific estimates; whenever significant heterogeneity was detected, the random effect model was used to address the heterogeneity across studies.[31] Subgroup analyses were conducted stratified by study location, prostate cancer stage, and potential confounders adjustments including a history of prostate-specific antigen (PSA) testing, a family history of prostate cancer, total energy intake, cigarette smoking, alcohol consumption, physical activity, body mass index (BMI), or history of diabetes. Since PSA testing was generally introduced after 1986,[32] studies with follow-up periods that ended before 1986 were classified in the PSA-adjusted group. To explore the influence of each study on the pooled results, sensitivity analyses were also performed by excluding one study at a time and then repeating the meta-analyzed approach.

We further examined the potential dose-response relationship between coffee consumption and the risk of prostate cancer. When the mean coffee intakes in each category were not reported, the midpoint values in each category were used instead; when the upper boundary of the highest intake category was not presented, we calculated the midpoint value assuming that highest category had the same magnitude of intake as the preceding category [33 34]. The pooled relative risk for each increment of 1 cups of coffee per day was estimated using the method proposed by Orsini and Greenland.[35] We examined a potential nonlinear relation between coffee consumption and prostate cancer risk by modelling coffee consumption using restricted cubic splines for nonlinear trends with 4 knots at fixed percentiles (5%, 35%, 65%, and 95%) of the distribution.[36] Non-linearity of the association was explored by testing the null hypothesis that the coefficients of the second and third splines were equal to zero.

We assessed the heterogeneity by using the Q and the I^2 statistic. A P value <0.10 or an I^2 >50% suggest statistical heterogeneity may exist.[37] Small study effects such as publication bias were evaluated by the funnel plots, as well as Begg's test and Egger's test.[38 39] Meta-analysis was conducted using the "*metan*" and "*glst*" commands in Stata version 14.0 (StataCorp LP, College Station, Texas). Two-sided P values of <0.05 were considered statistically significant in the meta-analysis.

RESULTS

Literature search

We identified 497 records after searching the three databases. After 217 duplicate records were removed, 280 records remained for titles and abstracts screening. After screening the titles and abstracts, 254 irrelevant records were excluded. After a further full-text review of the 26 remaining studies, ten studies were excluded because of no useful risk estimates or 95% CIs; two studies were excluded as newer data or more informative data were available. Fourteen studies were obtained from full-text screening. Besides, two studies were identified by checking the reference lists of retrieved articles [9 11]. Thus, we included 16 studies in the final analysis [9-11 13-19 21 24-28], of which 15 studies reported risk of prostate cancer associated with the highest versus the lowest coffee consumption [9-11 13-19 21 24-27]; 13 studies reported the risk associated with an increase of 1 cup of coffee per day or provided sufficient data to estimate the dose-response risk [9 13-19 21 24 25 27 28] **(Figure 1)**

Study characteristics and quality assessment

Characteristics of eligible cohort studies are showed in **Supplementary Document 4**. The included studies were conducted in North America (n=7), Europe (n=7), Japan (n=2). There was a total of 1,081,586 men in the 16 cohort studies, of whom 57,732 developed prostate cancer. To measure coffee consumption, 11 studies used food-frequency questionnaires and five used a self-administered dietary questionnaire. Most studies considered or adjusted for the most potential confounders in the analysis, such as age at baseline, family history of prostate cancer, race, cigarette smoking, alcohol drinking, total energy intake, body mass index (BMI), and physical activity, etc. Results of study quality assessment are presented in **Supplementary Document 5**. The total scores for each cohort study ranged from 6 to 9. Fourteen studies awarded a total score of ≥7, which were considered as relatively high-quality studies with low risk of bias.

Overall analyses and dose-response analyses

The reported RRs for the original cohort studies ranged from 0.47 (95%CI: 0.25, 0.87) for Pounis et al. study to 1.42 (95%CI: 0.77, 2.61) for Ellison et al. study (**Figure 2**). Compared with the lowest coffee intake category, there was a 9% reduction in the risk of prostate cancer for the highest category (RR=0.91; 95% CI: 0.84, 0.98). Statistically significant heterogeneity was detected across the studies (P=0.008, I^2=53.2%). In dose-response analyses, we found evidence of a linear inverse association between coffee consumption and prostate cancer risk (P=0.006 for linear trend) (**Figure 3**). The pooled RR of prostate cancer was 0.988 (95% CI: 0.981, 0.995) for an increase of 1 cup of coffee per day. No evidence of a nonlinear relationship was observed between coffee consumption and risk of prostate cancer (P=0.193 for non-linearity). Moreover, there was no indication of small study effects such as publication bias either from the results of Egger's test (P= 0.409), Begg's test (P= 0.843) as well as the funnel plot. Funnel plot and Egger's publication bias plot were shown in **Supplementary Document 6**.

Subgroup and sensitivity analyses

As presented in **Table 1**, compared with the lowest coffee intake category, there was a 7% reduction in risk for highest intake category (RR=0.93; 95% CI: 0.87, 0.99) for localized prostate cancer. For advanced and fatal prostate cancer, the corresponding pooled RRs were 0.88 (95% CI: 0.71, 1.09) and 0.84 (95% CI: 0.66, 1.08) (**Figure 4**). When stratified by study location, the pooled RRs were 0.96 (95%CI: 0.90, 1.03), 0.85 (95%CI: 0.74, 0.98) and 0.85 (95%CI: 0.48, 1.51) for studies conducted in North America (six in the United States and one in Canada), European countries and Japan. Besides, significant inverse associations were observed in all of the confounder adjusted subgroups.

In sensitivity analyses, we sequentially excluded one study at a time and recalculated the pooled RRs of the remaining studies. The pooled RRs did not change substantially, ranging from 0.89 (95% CI: 0.82, 0.97) to 0.93 (95% CI: 0.86, 1.00) after omissions of Hashibe et al. and Terdal et al., respectively.

245 **Table 1. Summary risk estimates and corresponding 95% confidence intervals for prostate**
246 **cancer associated with the highest verse lowest coffee consumption**

	No. of studies	Summary RR	95% CI	I^2 (%)	*P* value [a]
Overall	15	0.91	(0.84, 0.98)	53.2	0.008
Prostate cancer category [b]					
Localized	6	0.93	(0.87, 0.99)	37.0	0.159
Advanced	8	0.88	(0.71, 1.09)	52.7	0.039
Fatal	6	0.84	(0.66, 1.08)	46.3	0.097
Study location					
North America	7	0.96	(0.90, 1.03)	17.7	0.295
Europe	6	0.85	(0.74, 0.98)	63.3	0.018
Japan	2	0.85	(0.48, 1.51)	68.5	0.075
NOS score					
6	2	1.20	(0.84, 1.72)	0	0.507
7	3	1.02	(0.78, 1.32)	0	0.810
8 or 9	10	0.88	(0.81, 0.96)	66.2	0.002
Adjustment for confounders					
PSA testing [c]					
Yes	6	0.86	(0.77, 0.96)	31.8	0.197
No	9	0.94	(0.84, 1.06)	60.5	0.009
Family history of prostate cancer					
Yes	4	0.83	(0.72, 0.96)	57.8	0.068
No	11	0.95	(0.85, 1.05)	50.8	0.026
Total energy intake					
Yes	6	0.85	(0.76, 0.96)	61.1	0.025
No	9	0.97	(0.85, 1.09)	47.7	0.053
Smoking status					
Yes	10	0.86	(0.79, 0.94)	52.0	0.027
No	5	1.03	(0.95, 1.11)	0	0.805
Alcohol consumption					
Yes	6	0.87	(0.84, 0.98)	49.2	0.008
No	9	0.93	(0.84, 1.03)	57.2	0.017
Physical activity					
Yes	7	0.87	(0.79, 0.95)	58.4	0.025
No	8	1.00	(0.90, 1.12)	10.5	0.348
BMI					
Yes	9	0.86	(0.78, 0.94)	56.9	0.017
No	6	1.03	(0.95, 1.11)	0	0.897
Diabetes					
Yes	5	0.87	(0.84, 0.98)	64.9	0.022
No	10	0.97	(0.86, 1.10)	22.8	0.233

247 RR, relative risk; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen.
248 [a] *P*-value for heterogeneity within each subgroup.

[b] Based on definition in each original study, the prostate cancer categories were classified as follows: (i) localized prostate cancer which included localized or nonaggressive cancers, (ii) advanced prostate cancer which included advanced or aggressive cancers, (iii) fatal prostate cancer which included fatal/lethal cancers or prostate cancer specific deaths.

[c] Since PSA testing was generally introduced after 1986, studies with follow-up periods that ended before 1986 were classified in the PSA-adjusted group.

DISCUSSION

Summary of the findings

In this meta-analysis, higher coffee consumption was significantly associated with a reduced risk of prostate cancer in men. In the dose-response analysis, a nearly 1% reduction in risk of prostate cancer was observed for each increment of 1 cup of coffee per day. The combined estimate for prostate cancer was robust across subgroup and sensitivity analyses.

Comparison with other studies

The previous meta-analysis detected a statistically significant positive association between coffee consumption and prostate cancer risk (RR=1.16; 95% CI: 1.01, 1.33).[22] However, this observed effect was confined to the case-control studies (RR=1.21; 95% CI: 1.03, 1.43), and no significant association in the cohort studies (RR=1.06; 95% CI: 0.83, 1.35) when stratified by study design.[22] Considering the case-control design patients with prostate cancer might differentially recall their past coffee consumption habits compared to healthy controls which might generally lead to biased estimates. This potential recall bias could generate a spurious positive association between coffee consumption and prostate cancer risk. Additionally, selection bias which can occur in case-control studies may distort the association between coffee consumption and prostate cancer risk. In another meta-analysis of cohort studies with 539,577 participants and 34,105 prostate cancer cases, the pooled RR for the highest category of coffee intake was 0.90 (95% CI: 0.85-0.95) for total prostate cancer compared with the lowest intake category. In this updated meta-analysis of 1,081,586 cohort members and 57,732 incident cases, the overall result was similar with the previous one. However, for subgroups of localized, advanced and fatal prostate cancers, the strength of associations tended to be weaker compared with the previous study.

Possible biological mechanisms

It is biologically plausible that coffee may reduce the risk of prostate cancer in men. Coffee improves glucose metabolism, decreases concentrations of plasma insulin and insulin-like growth factors-1, has anti-inflammatory and antioxidant effects, and affects sex hormone levels, all of which may play roles in the initiation, development and progression of prostate cancer.[3 18 20 40] Coffee is also a major source of chlorogenic acids; intake of quinides, the degradation products of chlorogenic acids, has been observed to increase insulin sensitivity and lower blood glucose levels.[3] Moreover, coffee intake may be associated with increased levels of adiponectin plasma,[41 42] which may act as an endogenous insulin sensitizer.[43] Higher adiponectin in plasma were supposed to relate to lower concentrations of plasma insulin.[43] In two prospective studies, insulin levels were observed to be directly associated with prostate cancer specific mortality.[44 45]

Coffee is a major contributor of dietary antioxidants such as caffeic acid and chlorogenic acid.[20] A prospective cohort study from the United States found that dietary antioxidants from coffee, e.g. the caffeic acid, were inversely associated with risk of total, advanced and lethal prostate cancer.[20] It was suggested that antioxidants protect cells from damage caused by oxidative stress and inflammation, which may further lead to neoplastic transformation in the prostate.[46] Additionally, dietary antioxidants may inhibit prostate cancer progression through suppression of oxidative stress which might play a critical role during the progression of prostate cancer.[46] Coffee intake was indicated to be related to increased levels in sex hormone-binding globulin (SHBG), as well as total testosterone.[47 48] A pooled analysis of 18 prospective studies found that SHBG levels may be inversely associated with risk of prostate cancer.[40] Of note, a nested case-control study found that caffeine or caffeinated coffee intakes were suggested to be associated with an increased level of plasma SHBG. However, such association was not observed between decaffeinated coffee and plasma SHBG levels. Thus, it was suggested that caffeine may be the key component in coffee, which may be responsible for determining plasma SHBG levels.[48]

Strengths and limitations

A strength of this study was the inclusion of the prospective cohort studies. Cohort studies could minimize the risk of selection and recall bias, which is a major concern for case-control design. Besides, large numbers of total cohort members and prostate cancer cases ensure adequate statistical power to detect even a small effect of interest. Furthermore, the dose-response analysis may further lend confidence to the study hypothesis that increased coffee consumption was linearly associated with lower risk of prostate cancer. Besides, most of the studies were high-quality with low risk of bias, which could further lend confidence to the current pooled results.

This meta-analysis also has several limitations. First, one of the weakness is that only three databases were searched for eligible studies, and other databases, especially those non-English databases, were not considered in the literature search. Second, because of the observational design, unmeasured or uncontrolled confounders in the original studies may bias the pooled risk estimate; however, the residual confounding effects from the original studies were difficult to handle in a meta-analyzed approach.[49, 50] For example, the inverse association between coffee consumption and prostate cancer could be attributed to risk factors related to coffee consumption, such as physical activity and healthy diet. However, most of the original studies have considered or adjusted for these major potential confounders in the analysis. In the sensitivity analysis of restricting the meta-analysis in studies considering most confounders, the strength of association tended to be larger in comparison with the overall association. Third, misclassification of coffee consumption may occur because of the self-reported nature of exposure measurement. However, validation studies by diet records indicated a relatively high validity of coffee consumption measured by food frequency questionnaire. The correlations between questionnaire and diet records were 0.80 in US men,[16] 0.71 in Swedish men,[17] and 0.72 in Japanese men.[21] Of note, misclassification of exposure would most likely be non-differential in cohort studies and bias the observed association toward the null.[49, 50] Therefore, the true association between coffee consumption and risk of prostate cancer may be even stronger. Fourth, since the coffee intake and incidence of prostate cancer in the US and Europe are relatively high in these regions, most of the studies are conducted in these regions. Since the effect size is small, we should be cautious when generalizing the results to other areas, especially where the incidence is relatively low. Lastly, significant between-study heterogeneity may limit the result interpretation. The observed heterogeneity may come from various sources. For example, the highest and lowest category of coffee intake are different in the original studies. Study with a broader range between the highest and lowest category was assumed to generate a higher risk estimate. Moreover, the type of coffee and different brewing methods included in the coffee consumption groups differed. Besides, the different cohort size and follow-up periods may also lead to heterogeneous results. Taken together, due to the significant heterogeneity in the current meta-analysis, the pooled results should be interpreted with caution.

CONCLUSIONS

This study suggests that an increased coffee consumption may be associated with a reduced risk of prostate cancer. Further researches are still warranted to explore the underlying mechanisms and active compounds in coffee. If the association is further proven to be a causal effect, men might be encouraged to increase their coffee consumption to potentially decrease the risk of prostate cancer.

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AUTHOR CONTRIBUTIONS Kefeng Wang obtained the funding, developed the research design, interpreted the results, and also had primary responsibility for the final content; Xiaonan Chen, Yiqiao Zhao, Zijia Tao analyzed the data and interpreted the results; Xiaonan Chen and Kefeng Wang drafted manuscript; all authors critically reviewed and approved the manuscript.

COMPETING INTERESTS STATEMENT: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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DATA SHARING

The data are available upon reasonable request from the corresponding author (wangkefenguro@sina.com)

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Table

Table 1. Summary risk estimates and corresponding 95% confidence intervals for prostate cancer associated with the highest verse lowest coffee consumption

Figure legends

Figure 1 Flow diagram of study selection in the meta-analysis.

Figure 2 Forest plot for the association between coffee consumption and prostate cancer risk.

Figure 3 Dose-response relationship of coffee consumption with prostate cancer risk.

Figure 4 Forest plot for the association between coffee consumption and risk of prostate cancer stratified by cancer stages.

Supplementary Materials

Supplementary Document 1 PRISMA 2009 checklist.

Supplementary Document 2 MOOSE guidelines.

Supplementary Document 3 Search strategy for the meta-analysis

Supplementary Document 4 Characteristics of cohort studies of coffee consumption and prostate cancer risk included in the meta-analysis.

Supplementary Document 5 Quality of cohort studies included in the meta-analysis.

Supplementary Document 6 Funnel plot and Egger's publication bias plot for association between coffee consumption and prostate cancer risk**.**

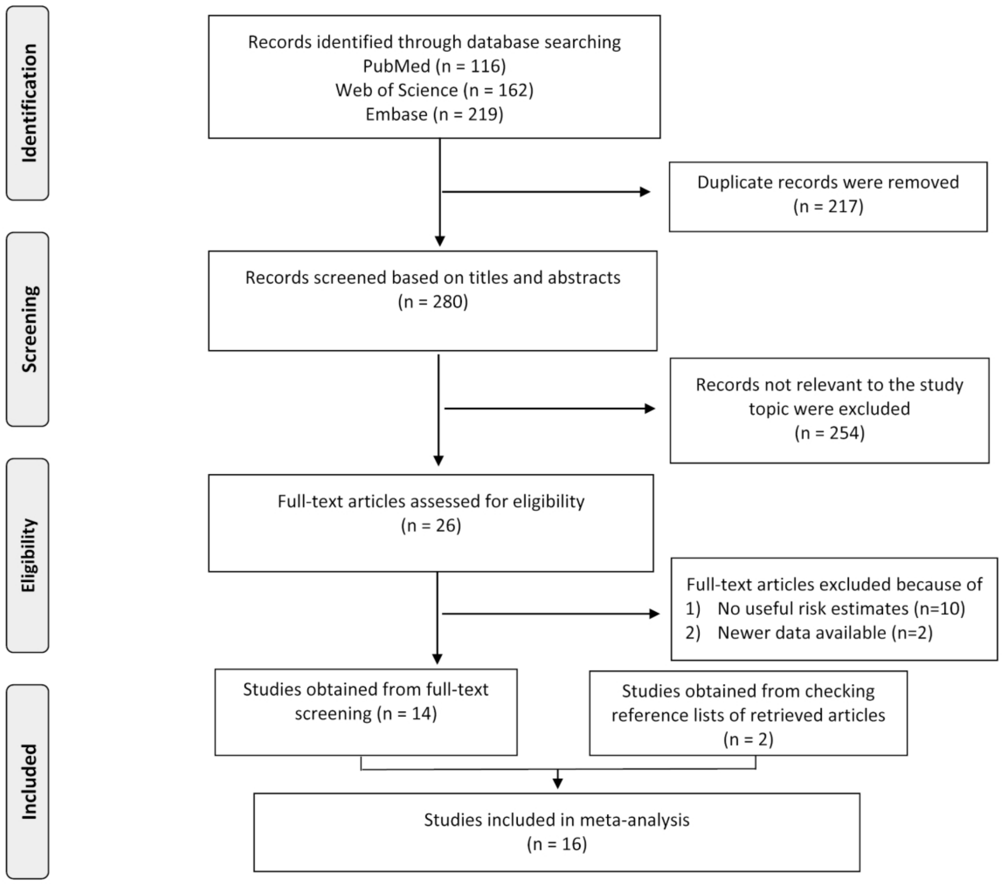

Figure 1 Flow diagram of study selection in the meta-analysis.

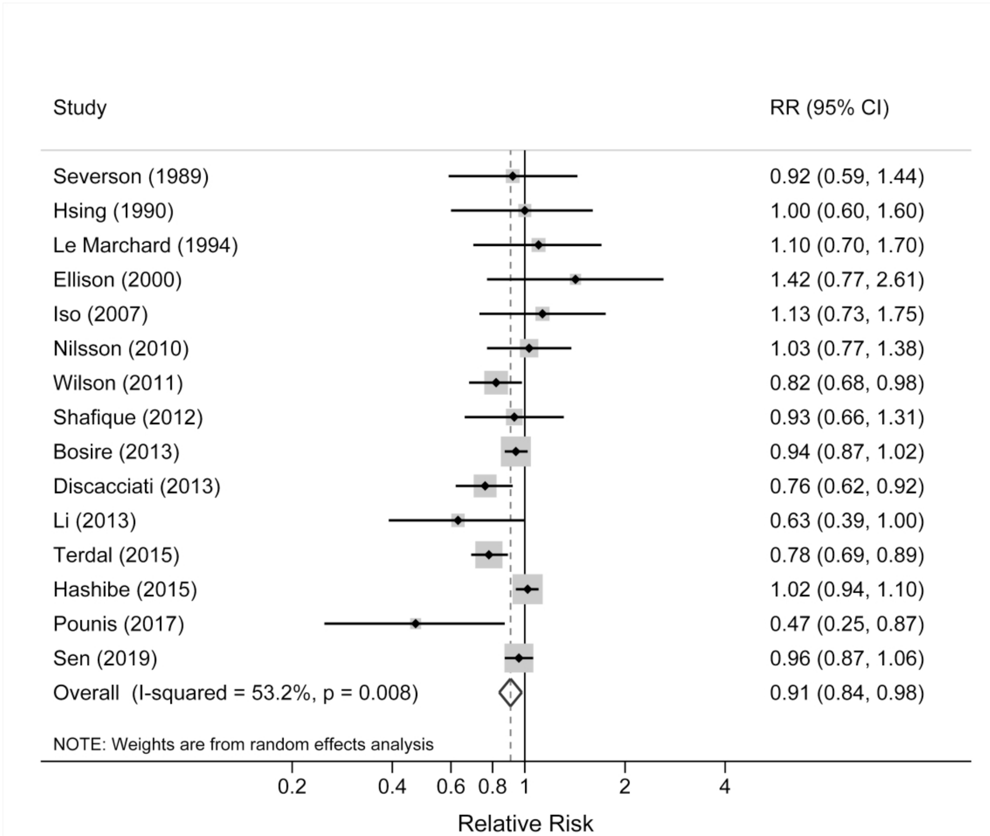

Figure 2 Forest plot for the association between coffee consumption and prostate cancer risk.

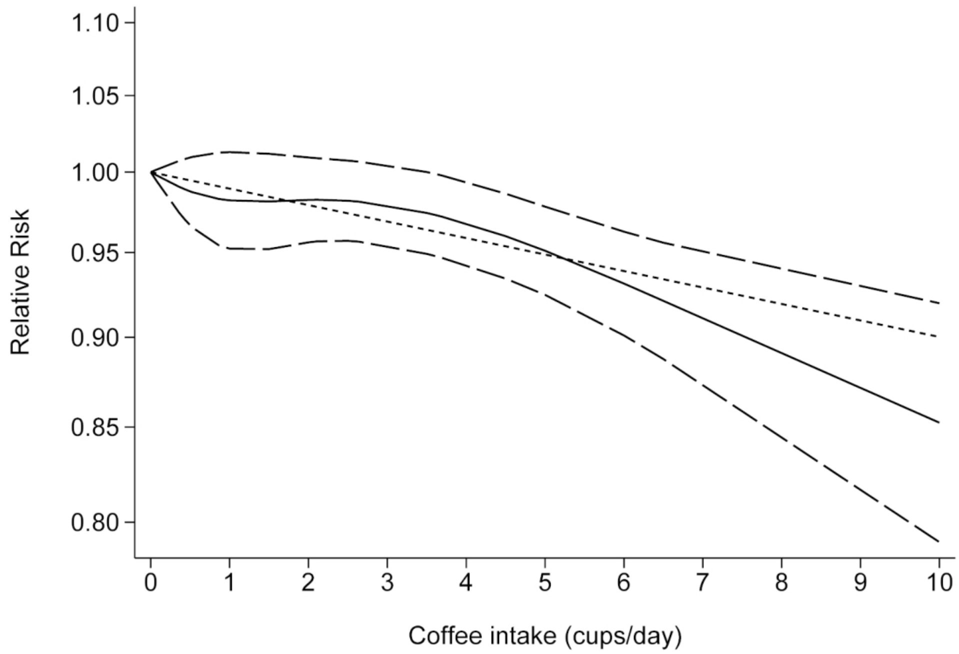

Figure 3 Dose-response relationship of coffee consumption with prostate cancer risk.

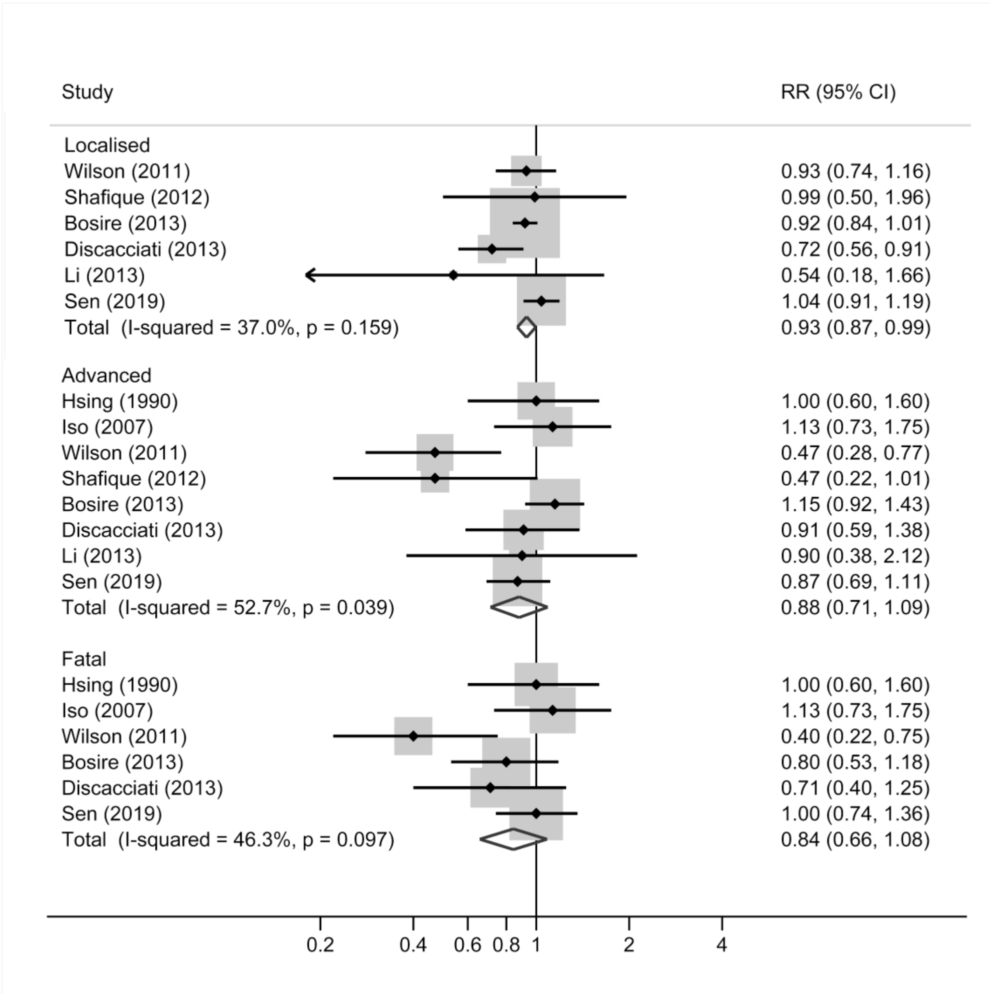

Figure 4 Forest plot for the association between coffee consumption and risk of prostate cancer stratified by cancer stages.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1, L1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P2, 3, L20-46
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P5, L84-87
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P5, L88-91
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P6, L104-125
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P7, L127-140
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P7, L127-13
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P6, L105-124
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P5, L97-98
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P7, 8, L142-148
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P8, L150-153
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P8,

PRISMA 2009 Checklist

			L155-156
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P8, 9, L156-188

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P9, L184-185
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P9, L170-182
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P10, L192-204
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P10, 11, L206-216
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P11, L215-216
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P11, L218-219
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P11, L220-227
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P11, L227-230
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P11, 12, L232-244
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P14, L259-263
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P17, 18, L322-354
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P18,

PRISMA 2009 Checklist

			L357-361
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P19, L364-366

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies*

	Topic	Page numbe
Title	Identify the study as a meta-analysis (or systematic review)	P1, L1-2
Abstract	Use the journal's structured format	P2-3, L20-40
Introduction	**Present:**	
	The clinical problem	P5, L84-87
	The hypothesis	P5, L87-88
	A statement of objectives that includes the study population, the condition of interest, the exposure or intervention, and the outcome(s) considered	P5, L88-90
Sources	**Describe:**	
	Qualifications of searchers (eg, librarians and investigators)	P5, L96
	Search strategy, including time period included in the synthesis and keywords	P7, L129-130
	Effort to include all available studies, including contact with authors	P7, L133-140
	Databases and registries searched	P7, L127-128
	Search software used, name and version, including special features used (e.g. explosion)	P7, L128-130
	Use of hand searching (e.g, reference lists of obtained articles)	P7, L130-131
	List of citations located and those excluded, including justification	NA
	Method of addressing articles published in languages other than English	NA
	Method of handling abstracts and unpublished studies	P7, L133-134
	Description of any contact with authors	P7, L133-140
Study Selection	**Describe**	
	Types of study designs considered	P6, L105-106
	Relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	P6,L105-124
	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	NA
	Documentation of how data were classified and coded (eg, multiple raters, blinding, and inter-rater reliability)	P5, L96-99
	Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate)	P8, L161-167
	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	P8, L149-153
	Assessment of heterogeneity	P9, L183-184
	Statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	P8-9, L155-188
Results	**Present**	
	A graph summarizing individual study estimates and the overall estimate	Figure 2
	A table giving descriptive information for each included study	Supplementary Document 4
	Results of sensitivity testing (eg, subgroup analysis)	P11-12, L231-244
	Indication of statistical uncertainty of findings	P11-12, L217-244
Discussion	**Discuss**	
	Strengths and weaknesses	P16-18, L312-353
	Potential biases in the review process (eg, publication bias)	P17, L324-341

	Assessment of quality of included studies	P17, L320-321
	Consideration of alternative explanations for observed results	P18, L344-346
	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	P18, L346-354
	Guidelines for future research	P18, L358-361
	Disclosure of funding source	P19, L364-366

*Modified from Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.

Pubmed (N=116)

Search date: up to Sep 21, 2020

Search terms:

("coffee"[MeSH Terms] OR "coffee"[All Fields] OR "coffee s"[All Fields] OR "coffees"[All Fields]) AND ("prostat"[All Fields] OR "prostate"[MeSH Terms] OR "prostate"[All Fields] OR "prostates"[All Fields] OR "prostatic"[All Fields] OR "prostatism"[MeSH Terms] OR "prostatism"[All Fields] OR "prostatitis"[MeSH Terms] OR "prostatitis"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields] OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields] OR "carcinoma s"[All Fields]) OR ("neoplasm s"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]))

Web of Science (N=162)

Search date: up to Sep 21, 2020

Search terms:

TOPIC: (coffee) AND TOPIC: (prostate) AND TOPIC: (cancer OR carcinoma OR neoplasm OR tumor) Indexes=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=All years

Embase (N=219)

Search date: up to Sep 21, 2020

Search terms:

coffee AND prostate AND (cancer OR carcinoma OR neoplasm OR tumor)

Table 1. Characteristics of cohort studies of coffee consumption and prostate cancer risk included in the meta-analysis

Study	Country	Study period	Age at baseline	Size of cohort/ controls	No. of cases	Exposure assessment methods	Definition of coffee consumption	Outcome	Follow-up time	Confounder adjustments	NOS total quality score; Risk of bias (Potential bias)
Ong et al. 2019	UK	2006-2010	37-73 years	131834	7532	Self-reported diet survey	1 cup/day increase; no information on the highest and lowest coffee intakes	Total prostate cancer	<5 years	Age, townsend deprivation index, top 10 ancestral principal components, smoking status, BMI, height, alcohol intake, drink temperature, overall heath rating, highest qualification. Instrumental variable analyses (SNP instruments) were also used to control confounders	7 stars; low risk of bias (exposure misclassification bias)
Sen et al. 2019	Europe	1990s-2015	Mean: 52 years.	142196	7036	Validated FFQ	The highest intake: median of 855 ml/day (no. of cases: 1271); The lowest intake: median of 0 ml/day (no. of cases: 396)	Total, Localized, advanced prostate cancer	Mean: 14 years	Stratified by center and age at recruitment in 5 years categories, and adjusted for smoking status, BMI, history of diabetes, alcohol intake, education, physical activity, energy intake, as well as calcium, fish, tea, fruit and vegetable intake.	9 stars; low risk of bias
Pounis et al 2017	Italy	2005-2010	⩾50 years;	6989	100	Validated FFQ	The highest intake: >3 cups/day (>90	Total prostate cancer	Mean: 4.24 years	Age, energy intake, smoking habits and BMI	8 stars; low risk of bias

			Mean: 67 years				g/day) (no. of cases: 14); The lowest intake: 0-2 cups/day (0-55 g/day) (no. of cases: 45)				
Hashibe et al. 2015	USA	1992-2011	55-74 years	46771	3037	Validated diet history questonnaire	Mean coffee intake is 1.9 cups/day; The highest intake: ≥2 cups/day (no. of cases: 1731); The lowest intake: <1 cups/day (no. of cases: 889)	Total prostate cancer	>10 years	Age, sex, race, and education.	8 stars; low risk of bias (confounding bias)
Tverdal et al. 2015	Norway	1974-1999	20-69 years	224234	5740	Questionnaire	The highest intake: ≥9 cups/day (no. of cases: 642); The lowest intake: none (no. of cases: 389)	Total prostate cancer	Mean: 17.6 years	Age, smoking, BMI, height, physical activity, total cholesterol, triglycerides, systolic blood pressure, year of examination and diabetes	8 stars; low risk of bias (exposure misclassification bias)
Li et al. 2013	Japan	1995-2005	40-79 years	18,853	318	Validated FFQ	The highest intake: ≥3	Total prostate	11 years	Age, education, BMI, time engaging in sports or exercise, marital status, time spent walking,	8 stars; low risk of bias

							cups/day (no. of cases: 24); The lowest intake: none (no. of cases: 84)	cancer incidence		smoking status, family history of cancer, job status, total energy intake, passive smoking, alcohol drinking, daily consumption of miso soup	
Discacciati et al. 2013	Sweden	1998-2010	45-79 years	44,613	3801	Validated self-administered FFQ	The highest intake: ≥6 cups/day (median of 1484 g/day) (no. of cases: 173); The lowest intake: none (median: 0 g/day) (no. of cases: 129)	Localized and advanced prostate cancer incidence Prostate cancer mortality	13 years	Age, tea, alcohol, BMI, diabetes, family history of prostate cancer, smoke, physical activity, education, total energy intake.	8 stars; low risk of bias
Bosire et al. 2013	USA	1995-2008	50-71 years	288,391	23335	Validated FFQ	The highest intake: ≥6 cups/day (no. of cases: 787); The lowest intake: none (no. of cases: 2136)	Total prostate cancer incidence	>11 years (median: 10.5 years)	Age, race, height, BMI, physical activity, smoking, history of diabetes, family history of prostate cancer, PSA testing, intakes of tomato sauce, alpha-linolenic acid, and total energy intake.	8 stars; low risk of bias
Shafique et al. 2012	UK	1970-2007	21-75 years (median	6017	318	Self-administered questionnaire	The highest intake: ≥3 cups/day (no. of cases: 65);	Total prostate cancer incidence	37 years (median: 28 years)	Age at screening, cholesterol, systolic blood pressure, BMI, alcohol intake, tea consumption, smoking status, social class.	8 stars; low risk of bias (exposure misclassification bias)

			: 48 years)				The lowest intake: none (no. of cases: 139)				
Wilson et al. 2011	USA	1986-2006	40-75 years	47,911	5035	Validated FFQ	The highest intake: ≥6 cups/day (no. of cases: 152); The lowest intake: none (no. of cases: 587)	Total prostate cancer incidence	20 years	Age in months, calendar time, race, BMI at age 21, current BMI, vigorous physical activity, smoking, diabetes, family history of prostate cancer in father or brother, multivitamin use, intakes of processed meat, tomato sauce, calcium, alpha-linolenic acid, supplemental vitamin E, alcohol intake, energy intake, history of PSA testing.	9 stars; low risk of bias
Nilsson et al. 2010	Sweden	1985-2007	40-60 years (median : 50 years)	30,930	653	Validated Semi-quantitative FFQ	The highest intake: ≥4 cups/day (no. of cases: 209); The lowest intake: <1 cup/day (no. of cases: 60)	Total prostate cancer incidence	15 years (median: 6 years)	Age, BMI, smoking, education, recreational physical activity.	8 stars; low risk of bias
Iso et al. 2007	Japan	1988-1997	40-79 years	43,500	161	Self-administrated questionnaire	The highest intake: ≥2 cups/day (no. of cases: 38);	Prostate cancer mortality	Mean: 8.15 years	Age, area of study	7 stars; low risk of bias (exposure misclassification bias, confounding bias)

							The lowest intake: ⩽1-2 cup/month (no. of cases: 47)				
Ellison et al. 2000	Canada	1970-1993	50-84 years	3400	145	FFQ	The highest intake: ≥750 mg/day (no. of cases: 122); The lowest intake: 0 mg/day (no. of cases: 23)	Total prostate cancer incidence	Mean: 11.6 year	Age, wine consumption.	6 stars; medium risk of bias (exposure misclassification bias, confounding bias)
Le Marchand et al. 1994	USA	1975-1989	⩾45 years	20,316	198	Self-administered life-style questionnaire	The highest intake: ≥2.5 cups/day; The lowest intake: none.	Total prostate cancer incidence	Median: 6 years	Age, ethnicity, income.	6 stars; medium risk of bias (exposure misclassification bias, confounding bias)
Hsing et al. 1990	USA	1966-1986	⩾35 years (Median : 51 years)	17,633	149	FFQ	The highest intake: ≥5 cups/day; The lowest intake: <3 cups/day.	Prostate cancer mortality	20 years (Mean: 15.6 years)	Age, tobacco use.	7 stars; low risk of bias (exposure misclassification bias, confounding bias)
Severson et al. 1989	USA	1965-1986	46-68 years	7998	174	FFQ + 24-h diet recall interview	The highest intake: ≥5 cups/week (no. of cases: 146);	Total prostate cancer incidence	Mean: 17.4 years	Age	7 stars; low risk of bias (confounding bias)

The lowest intake: <1 cups/week (no. of cases: 22)

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; NA, not available; PSA, prostate-specific antigen; RR, relative risk;

Supplementary Table S3 Quality of cohort studies included in the meta-analysis

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Controls for important risk factors [1]	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total quality score
Ong et al. 2019	☆	☆	–	☆	☆☆	☆	–	☆	7
Sen et al. 2019	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Pounis et al 2017	☆	☆	☆	☆	☆☆	☆	–	☆	8
Hashibe et al. 2015	☆	☆	☆	☆	☆	☆	☆	☆	8
Terdal et al. 2015	☆	☆	–	☆	☆☆	☆	☆	☆	8
Li et al. 2013	☆	☆	☆	☆	☆☆	☆	☆	–	8
Discacciati et al. 2013	☆	☆	☆	☆	☆☆	☆	☆	–	8
Bosire et al. 2013	☆	☆	☆	☆	☆☆	☆	☆	–	8
Shafique et al. 2012	☆	☆	–	☆	☆☆	☆	☆	☆	8
Wilson et al. 2011	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Nilsson et al. 2010	☆	☆	☆	–	☆☆	☆	☆	☆	8
Iso et al. 2007	☆	☆	–	☆	☆	☆	☆	☆	7
Ellison et al. 2000	☆	☆	–	☆	☆	☆	☆	–	6
Le Marchand et al. 1994	☆	☆	–	☆	☆	☆	☆	–	6
Hsing et al. 1990	☆	☆	–	☆	☆	☆	☆	☆	7
Severson et al. 1989	☆	☆	☆	☆	☆	☆	☆	–	7

1. A maximum of 2 stars could be awarded for this item. Studies that included adjustment for age received one star, and studies that included most of the other important confounders such as ethnicity, dietary factors (energy intake, vitamin D, dietary fat etc.), physical activity, body mass index, type 2 diabetes mellitus, alcohol and smoking received an additional star.

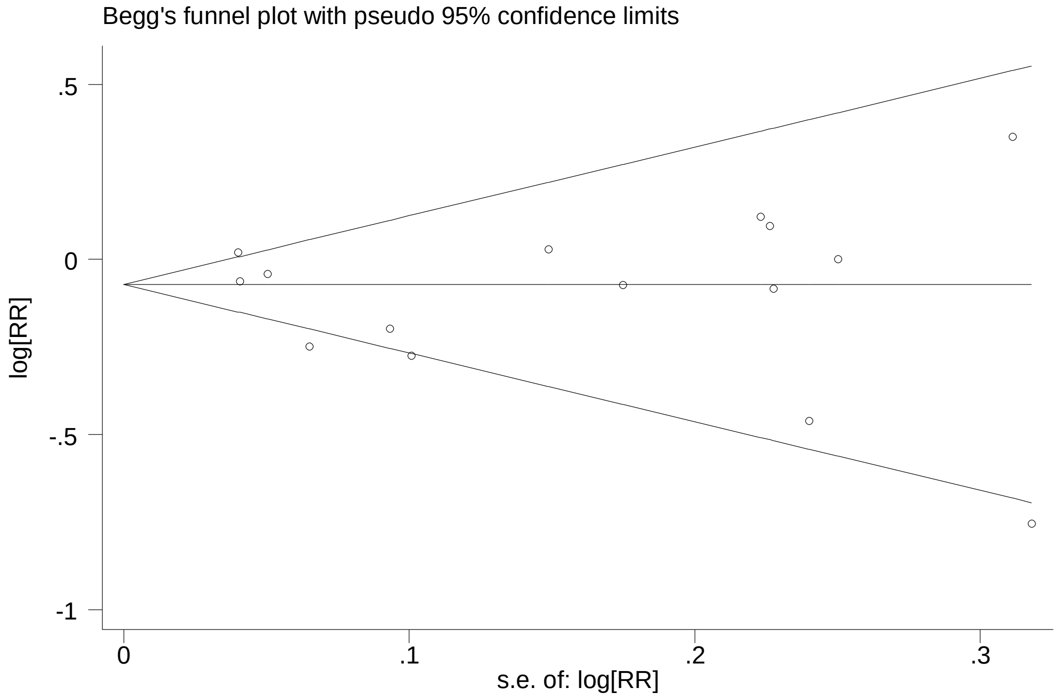

Figure S1 Begg's funnel plot of coffee consumption and prostate cancer risk

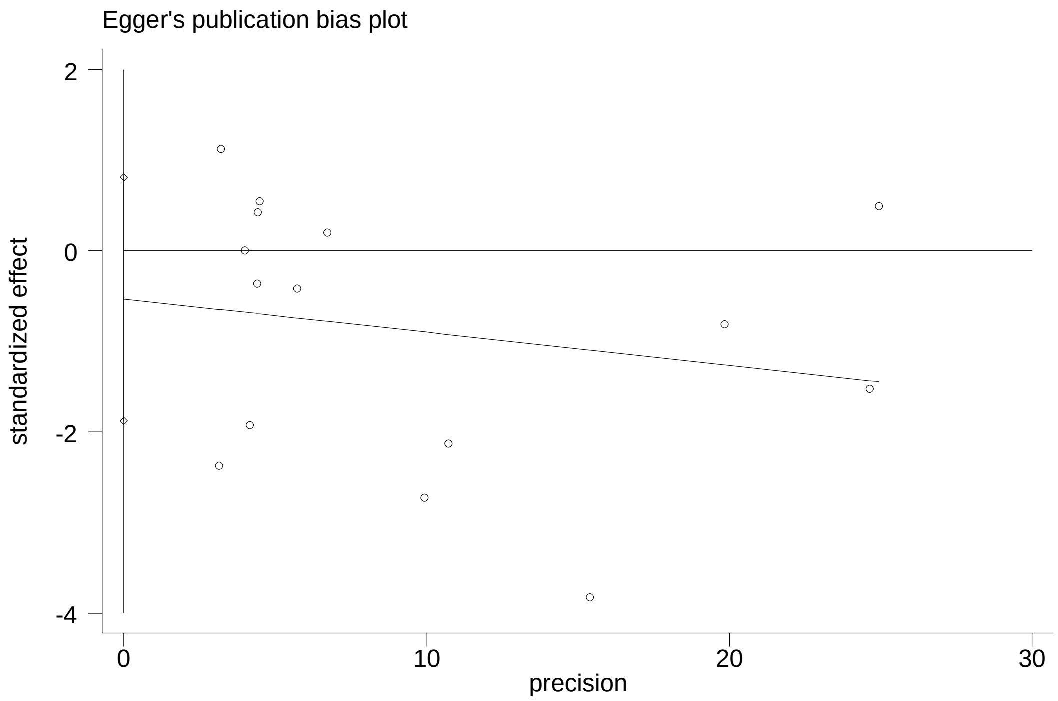

Figure S2 Egger's publication bias plot of coffee consumption and prostate cancer risk